Bilirubin and Serial Auditory Brainstem Responses in Premature Infants

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ABSTRACT. *Objectives.* **To determine the usefulness of the bilirubin-albumin (B:A) molar ratio (MR) and unbound bilirubin (UB) as compared with serum total bilirubin (TB) in predicting bilirubin encephalopathy as assessed by auditory brainstem responses (ABR) in infants of 28 to 32 weeks' gestational age.**

Study Design. **During a 2-year period, serial ABRs were obtained on 143 infants of 28 to 32 weeks' gestational age during the first postnatal week. Waveforms were categorized on the basis of response replicability and the presence of waves III and V. Wave V latencies were also serially analyzed when measurable for individual infants. Maturation of the ABR was defined as abnormal when the waveform category worsened and/or latency increased during the study interval. Serum albumin was analyzed at 48 to 72 hours of age in all patients. Serum TB was analyzed as clinically indicated. Aliquots of the same samples were also analyzed for UB in a subset of infants.**

Results. **The mean peak TB concentration (10.1 ± 1.7 mg/dL) for the 71 infants with normal ABR maturation was not significantly different from the mean peak TB (10.2 ± 2.1 mg/dL) in the 24-hour period preceding the ABR's first showing abnormal maturation in the other 55 infants. However, in infants with UB analyzed, the mean peak UB (0.62 ± 0.20 vs 0.40 ± 0.15 μg/dL) was significantly higher in the infants with abnormal maturation ($n = 25$) than in infants with normal maturation ($n = 20$). The B:A MR results were equivocal. In the entire study population, there was no difference in B:A MR between infants with normal versus abnormal ABR maturation. However, in the subset of infants in whom UB was measured, although TB was not different, there was a significant difference in B:A MR. Based on receiver-operating characteristic curves, a UB level of 0.5 μg/dL was the best discriminator with a sensitivity of 70% and a specificity of 75%. The proportion of infants who had UB >0.5 μg/dL and UB ≤0.5 μg/dL and who had abnormal ABR, maturation was 0.81 and 0.33, respectively, with a significant difference in the incidence of transient bilirubin encephalopathy among these 2 groups. The relative risk of abnormal ABR maturation with UB >0.5 μg/dL compared with UB ≤0.05 μg/dL was 2.45 (95% confidence interval: 1.33–4.49).**

Conclusions. **UB is a more sensitive predictor than either serum bilirubin or B:A MR of abnormal ABR maturation, and hence transient bilirubin encephalopathy in premature newborns with hyperbilirubinemia.** *Pediatrics* **2001;107:664–670;** ***bilirubin-albumin molar ratio, unbound bilirubin, auditory brainstem-evoked response, response types.***

ABBREVIATIONS. TB, total bilirubin; ABR, auditory brainstem response; UB, unbound bilirubin; B:A, bilirubin-albumin; MR, molar ratio; GA, gestational age; ROC, receiver-operating characteristic; SD, standard deviation.

Kernicterus often occurs at lower serum total bilirubin (TB) concentrations in premature newborns as compared with term newborns.[1–6] Furthermore, premature newborns may not exhibit the acute neurologic signs of bilirubin encephalopathy seen in term newborns. Because the TB concentration is an unreliable predictor of bilirubin encephalopathy in the premature newborn,[1,7,8] alternative means for detecting bilirubin encephalopathy in jaundiced preterm newborns is needed. Bilirubin has specific predilection for the auditory neural pathways; therefore, early detection of bilirubin-induced neuronal injury may be possible by the use of auditory brainstem responses (ABRs).[9–13]

ABR changes induced by bilirubin progress from reversible prolongation of the absolute latencies of waves III and V followed by loss of wave amplitude and ultimately the inability to detect an identifiable wave.[9–11,14] These reversible changes may persist for up to 24 hours after the decrease in serum TB concentrations. Furthermore, prolonged bilirubin toxicity may cause irreversible sensorineural hearing loss.[15–17]

The pathogenesis of bilirubin encephalopathy is complex. Clinical factors, bilirubin-albumin binding, and the integrity of the blood-brain barrier all are thought to play significant roles in bilirubin toxicity. Current data support the notion that unbound bilirubin (UB; also referred to as nonalbumin bound or free bilirubin) is capable of crossing the intact blood-brain barrier and causing subsequent neuronal damage.[18] In term newborns, UB has been reported to be a more sensitive predictor of bilirubin encephalopathy as evaluated by ABR than either serum bilirubin or the bilirubin-albumin (B:A) molar ratio (MR).[11,12] However, in the premature infant, the usefulness of bilirubin-albumin binding variables has not been demonstrated clearly, and there are conflicting data regarding the association of UB and kernicterus in this population. Cashore[19,20] and Nakamura et al[8] reported significantly elevated mean UB levels in

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premature infants with kernicterus, whereas Ritter et al[21] in a prospective study found that neither TB concentration nor UB levels identified infants with and without kernicterus. However, TB levels were very low and UB levels were very high in most infants studied, suggesting the presence of bilirubin-albumin binding competitors in the population.

The current study was designed to determine the usefulness of the B:A MR and UB as compared with routinely used serum TB in predicting bilirubin encephalopathy as assessed by ABR in premature newborns of 28 to 32 weeks' gestational age (GA).

PARTICIPANTS AND METHODS

All newborns, 28 to 32 weeks' GA, who were admitted to the neonatal intensive care unit of the Children's Hospital at Strong (Rochester, NY) from July 1996 to July 1998 were eligible for the study. GA was assessed by obstetric dating when available and otherwise by Ballard examination. Exclusion criteria included hypothermia, chromosomal abnormalities, TORCH infections (toxoplasmosis, other infections, rubella, cytomegalovirus infection, and herpes simplex), and instability for baseline testing. The assessment of the stability of the patient was at the discretion of the attending neonatologist. Phototherapy was used according to the institutional protocol for management of hyperbilirubinemia in premature infants. Risk factors thought to enhance susceptibility to bilirubin encephalopathy (Apgar score <5 at 5 minutes, clinical sepsis, intraventricular hemorrhage grades 3 and 4, maternal-fetal blood group incompatibility with a positive Coombs test, Pco_2 >60 torr, Pao_2 <45 torr, and pH <7.25) were recorded for each patient during the study period. The study was approved by the University of Rochester Institutional Review Board.

Auditory Brainstem Response

After parental consent was obtained, sequential bilateral monaural ABRs were performed by skilled audiologists on 5 of the first 7 days of life, with the first ABRs obtained within 24 hours of age. ABRs were recorded using a Biological Navigator Evoked Response Recorder (Bio-logic Corporation, Mundelein, IL) with the infant lying supine in the isolette with skin temperature ≥35.5°C and with his or her head turned to the side. After gel was applied to the silver/silver chloride electrodes, they were placed on the mastoid (reference), high on the midline of the forehead or crown (active), and the shoulder (ground). Monaural ABR testing was performed on each ear using 80 dB nHL alternating broadband click stimuli presented to the ear by holding a TDH-39 earphone over the ear. The response was amplified (× 200 000) and band-pass filtered (100–3000 Hz) and averaged over a 20-msec time epoch. The clicks were presented at a repetition rate of 39.9/sec, and 3 runs of 2000 repetitions were recorded for each ear. The 2 most reproducible runs for each ear were averaged and used for analysis.

The recorded ABRs were analyzed by skilled audiologists without knowledge of GA, previous ABR results, or serum TB concentrations. The ABRs were categorized into the following response types on the basis of reproducibility and presence of waves III and V (Fig 1) as previously described[22]: type 1, a response with normal morphology and replicable waves III and V; type 2, a replicable response with either a wave III or a wave V (but not both); type 3, a replicable response with neither a wave III nor a wave V; and type 4, a response with no replicable waveform. We previously demonstrated that with advancing GA and chronological age, response type matures from type 4 to type 1 and the absolute latencies shorten.[22] For analysis, the response from the better ear (lower response type or shorter absolute latencies) was used. For each infant, sequential ABRs were classified by the audiologists as normal or abnormal maturation without knowledge of GA or serum TB concentration. Normal day-to-day ABR maturation in an individual infant was characterized by an improvement in response type (eg, type 2 to type 1) or shortening wave V latency. Conversely, abnormal ABR maturation was characterized by a deterioration in response type (eg, from type 1 to type 2) or prolongation of wave V latency compared with the previous ABRs. Maturation was considered equivocal when the ABRs showed no change in either variable over time.

Bilirubin-Albumin Binding Variables

Blood samples for the measurement of TB and UB were drawn as clinically indicated at the discretion of the attending neonatologists, who were unaware of the ABR findings. Serum TB and albumin levels were measured by the clinical laboratory using standard colorimetric methods. Because the half-life of serum albumin is ~3 weeks, a single serum albumin level for each patient was drawn between 48 and 72 hours of age and used for determining B:A MRs. UB concentrations were measured by the peroxidase method[23] using an Arrows UB Analyzer UA-1 (Arrows Co, Ltd., Osaka, Japan) from the same aliquots of blood used to measure serum TB. Sera were protected from light and stored at −80°C until analyzed for UB within 1 hour of thawing. We have found that UB measurements in serum or plasma are not altered by a single freeze (−80°C) and thaw.

Statistical Analysis

Statistical analysis was performed using Stata program (Stata Corporation, College Station, TX). Student's t test was used to analyze continuous variables. χ^2 was used to analyze nominal variables. $P \leq .05$ was considered significant. The sensitivity and specificity of bilirubin-albumin binding variables as predictors of abnormal ABRs were assessed using relative ratios and receiver-operating characteristic (ROC) curves.

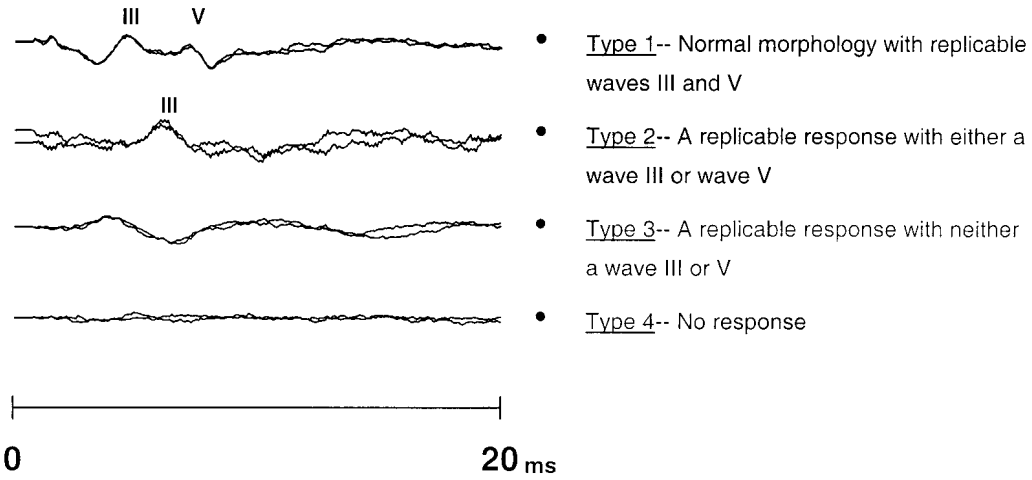

Fig 1. Wave form response types 1 through 4.

RESULTS

Total Population

During the study period, 257 infants, 28 to 32 weeks' GA, were admitted to the intensive care unit. Thirty-six were excluded on the basis of predefined criteria. A total of 143 infants were enrolled; of these, 3 withdrew from the study after the first 2 days, 8 had equivocal ABR maturation, and 6 had less than 2 days of bilirubin data and were excluded from additional analysis. The demographics, risk factors, and albumin concentrations of the remaining 126 infants are given in Table 1. All infants survived the hospital stay without overt signs of kernicterus.

The 5 ABRs for each premature infant were obtained a mean of 27 hours (standard deviation [SD 3.8]) apart. The ABR response types, wave V latencies, and number of premature infants demonstrating normal ABR maturation compared with the previous measurement are given in Table 2. Overall, 71 of 126 infants (56%) demonstrated normal ABR maturation over the entire study period. Maturation was deemed abnormal in 55 infants (12 infants between tests 1 and 2, 23 infants between tests 2 and 3, 14 infants between tests 3 and 4, and 6 infants between tests 4 and 5).

The mean, SD, and ranges of highest TB concentrations that occurred in the 24-hour period preceding each ABR measurement as a function of ABR response type and maturation are given in Table 3. There was no significant difference in mean TB concentration (and B:A MRs) as a function of ABR maturation for any given ABR epoch. Similarly, the mean peak TB concentration and B:A MR measured during the entire study period for the 71 infants with normal ABR maturation were not significantly different from the mean peak bilirubin and B:A MR measured in the 24 hours that preceded the ABR that first showed abnormal maturation in the other 55 infants (10.1 mg/dL [SD 1.7] vs 10.2 mg/dL [SD 2.1], $P = .68$; and 0.37 mg/dL [SD 0.08] vs 0.39 mg/dL [SD 0.09], $P = .19$). The wave V latencies and response types at the time of these peak bilirubin measurements, however, were significantly different (8.82 msec [SD 0.85] vs 9.85 msec [SD 1.06], $P < .001$; and 2.5 vs 3, $P < .001$, normal vs abnormal maturation, respectively).

The lack of correlation between peak bilirubin levels and abnormal ABR maturation indicates that either the TB is not a sensitive indicator of miscible bilirubin pool size or the ABR changes are not caused by bilirubin. The UB measurement was used to address this issue.

Subgroup With UB Determination

UB was measured in a subgroup of the entire population (45 of 126). The demographics, risk factors, and albumin concentrations for this subgroup (Table 1) did not differ significantly from the entire group ($n = 126$) or when the 45 infants were grouped according to ABR maturation. The mean, SD, and ranges of highest UB, as well as serum TB and B:A MR occurring in the 24-hour period that preceded each ABR measurement as a function of ABR maturation, are given in Table 4. As compared with serum TB, UB differed significantly between the infants with normal and abnormal ABR maturation.

The peak TB and UB concentrations and B:A MRs for the subgroups with normal and abnormal ABR maturation were determined as described above for the entire population. The results are given in Table 5. Both the mean peak UB and B:A MR were significantly higher in the infants with abnormal maturation, whereas the mean peak TB was not significantly different. This is highly suggestive that abnormal ABR maturation is associated with bilirubin and best predicted by bilirubin binding rather than the TB.

ROC curves were plotted to compare TB and UB as predictors of abnormal ABR maturation and by inference transient bilirubin encephalopathy (Fig 2). These ROC curves indicate that UB is a more sensitive and specific predictor of transient bilirubin encephalopathy than is TB. On the basis of ROC curves, it was determined that a UB level of 0.5 μg/dL provided the best sensitivity (70%) and specificity (75%). Eighty-one percent of those patients with UB >0.5 μg/dL had an abnormal ABR maturation, compared with only 33% of those with a UB ≤ 0.5 μg/dL ($P < .05$). The relative risk of abnormal ABR maturation if the UB was >0.5 μg/dL compared with a UB ≤ 0.05 μg/dL was 2.45 (95% confidence interval: 1.33–4.49).

TABLE 1. Demographics, Risk Factors, and Albumin of the Study Population

	Total	Normal ABR Maturation		Abnormal ABR Maturation	
		Total	UB Measured	Total	UB Measured
n	126	71	20	55	25
Gestational age (wk)*	30.3 (1.2)	30.5 (1.1)	30.1 (1.1)	30.1 (1.2)	29.9 (1.2)
Birth weight (g)*	1439 (314)	1479 (327)	1359 (314)	1388 (292)	1333 (318)
Male/female (*n*)	67/59	38/33	9/11	29/26	13/12
Apgar <5 (*n*)	9 (7%)	3 (4%)	0	6 (11%)	2 (8%)
Hemolysis (*n*)	5 (4%)	2 (3%)	2 (10%)	3 (5%)	3 (12%)
Sepsis (*n*)	37 (29%)	18 (25%)	4 (20%)	19 (35%)	9 (36%)
Pco_2 >60 (*n*)	4 (3%)	1 (1%)	0	3 (5%)	2 (8%)
pH <7.25 (*n*)	13 (10%)	6 (8%)	2 (10%)	7 (13%)	5 (20%)
Po_2 <45 (*n*)	0	0	0	0	0
IVH >II (*n*)	1 (.8%)	1 (1.4%)	0	0	0
Albumin (g/dL)*	3 (0.44)	3 (0.43)	3.1 (0.46)	2.9 (0.45)	2.9 (0.46)

IVH indicates intraventricular hemorrhage; *n*, number of infants.
* Mean (standard deviation).

TABLE 2. Wave V Latencies, Response Types, and ABR Maturation

	ABR Number				
	1	2	3	4	5
Wave V latency (msec)					
n	70	80	89	99	108
Mean (SD)	9.52 (0.91)	9.08 (0.89)	9.12 (0.97)	9.03 (0.94)	8.9 (0.93)
Range	6.94–11.62	7.02–12.17	7.25–12.09	7.33–11.86	6.94–12.25
Response type					
1	55	76	84	93	108
2	25	13	14	13	9
3	32	26	18	16	5
4	14	11	10	4	4
Maturation Normal		114/126	91/126	77/126	71/126

n indicates number of infants.

TABLE 3. Total Bilirubin (mg/dL), ABR Maturation, and ABR Response

	Total (n = 126)	ABR Maturation		Response Type			
		Normal (n = 71)	Abnormal (n = 55)	1	2	3	4
ABR 1							
n		NA	NA	55	25	32	14
Mean (SD)	6 (1.9)			6.2 (1.7)	6.6 (1.7)	6.2 (2.2)	4.7 (2.1)
Range	2.7–10.1			4.3–10.1	3.6–9	2.7–9.1	2.8–7.2
ABR 2							
n				76	13	26	11
Mean (SD)	8.3 (2.1)	8.2 (2.3)	8.5 (1.9)	8.4 (2.1)	9.1 (2.8)	7.7 (1.6)	8.3 (2.2)
Range	3.1–14.2	3.1–14.2	4–13.9	3.1–14.2	6.5–13.9	4–11.3	5.6–11.3
ABR 3							
n				84	14	18	10
Mean (SD)	9.3 (2.2)	9.2 (2.4)	9.5 (1.9)	9.4 (2.4)	9.0 (1.1)	9.2 (1.7)	9.6 (2)
Range	1.5–14.5	1.5–14.1	5.2–14.5	1.5–14.5	7.1–11	5.5–12.7	6.1–12.6
ABR 4							
n				93	13	16	4
Mean (SD)	8.9 (2)	8.9 (1.8)	9.0 (2.2)	9.1 (1.9)	7.8 (1.8)	8.6 (2.2)	9.2 (1.9)
Range	4.4–14.1	4.4–13.7	4.4–14.1	4.4–14.1	5.8–11.8	4.4–11.4	7.4–11.8
ABR 5							
n				108	9	5	4
Mean (SD)	8 (2)	7.8 (1.8)	8.3 (2.1)	8 (2)	7.4 (1.1)	7.6 (1.8)	8 (2.9)
Range	3.7–13	3.7–11.6	4.6–13	3.7–13	6.1–9.1	4.9–8.6	5.7–11.9

n indicates number of infants.

DISCUSSION

Serum TB remains the primary biochemical measure used to evaluate and treat premature newborns with hyperbilirubinemia, although there is substantial evidence that serum TB levels correlate poorly with bilirubin-induced neurotoxicity in the premature infant.[7,24–29] Moreover, institutional variations in the levels of bilirubin at which phototherapy and exchange transfusions are initiated in jaundiced premature newborns indicate that the current management of hyperbilirubinemia in these infants is not evidence based.[30] Our study demonstrates that UB is a more sensitive predictor of bilirubin-induced auditory toxicity as evaluated by ABR changes than either B:A MR or serum TB levels in newborns of 28 to 32 weeks' GA.

The results of this study and several others provide UB concentrations in premature newborns associated with either overt kernicterus or transient bilirubin encephalopathy as indicated by ABR changes. A progression of bilirubin neurotoxicity seems to correlate with UB levels. In term newborns, UB levels must increase to 1 to 2 μg/dL before bilirubin-induced ABR changes are likely.[12] In the premature infant, ABR changes appear as the UB concentration exceeds 0.5 μg/dL, and overt kernicterus becomes likely above a UB of 1 μg/dL[8,20,21] (Table 6).

Bilirubin binding is a complex function of the concentrations of TB, UB, and albumin. Although the B:A MR is a measure of bilirubin binding and was a significant predictor of ABR abnormalities in the subgroup of premature neonates who had UB measurements, the ratio did not significantly predict abnormal ABR maturation in the entire population (P = .19). The trend, however, was better than that for the TB (P = .98). Although this supports the measurement of UB as the best predictor of bilirubin toxicity, the data do illustrate the potential value of at least considering the B:A MR along with the TB when UB measurements are not available.

Several in vitro and in vivo studies demonstrated that bilirubin-induced neurotoxicity involves changes in energy metabolism, alteration in membrane function, decreased membrane potential, alteration in enzyme function, and inhibition of protein and DNA synthesis.[31,32] It also seems from in vitro studies that immature cells are more sensitive to bilirubin toxicity than differentiated cells, supporting

TABLE 4. UB (μg/dL), SB (mg/dL), Bilirubin-Albumin MR, and ABR Maturation

	Total (n = 45)	ABR Maturation	
		Normal (n = 20)	Abnormal (n = 25)
ABR 1			
UB			
Mean (SD)	0.26 (0.12)	–	–
Range	0.07–0.46		
TB			
Mean (SD)	6.8 (1.7)		
Range	2.8–10.1		
MR			
Mean (SD)	0.28 (0.08)		
Range	0.14–0.44		
ABR 2			
UB			
Mean (SD)	0.40 (0.20)	0.29 (0.12)	0.48 (0.21)
Range	0.08–0.96	0.08–0.5	0.13–0.96
TB			
Mean (SD)	8.2 (1.9)	7.2 (2.1)	8.8 (1.6)
Range	3.1–11.3	3.1–10.9	5.6–11.3
MR			
Mean (SD)	0.32 (0.09)	0.26 (0.09)	0.35 (0.07)
Range	0.08–0.48	0.08–0.48	0.21–0.48
ABR 3			
UB			
Mean (SD)	0.46 (0.21)	0.33 (0.14)	0.54 (0.22)
Range	0.06–0.97	0.06–0.59	0.14–0.97
TB			
Mean (SD)	9.1 (2)	8.8 (2.4)	9.4 (1.6)
Range	2.7–12.8	2.7–12.6	5.5–12.8
MR			
Mean (SD)	0.35 (0.08)	0.31 (0.09)	0.37 (0.07)
Range	0.06–0.59	0.06–0.43	0.24–0.59
ABR 4			
UB			
Mean (SD)	0.37 (0.20)	0.32 (0.20)	0.43 (0.19)
Range	0.01–1.01	0.01–0.73	0.23–1.01
TB			
Mean (SD)	8.8 (1.7)	8.6 (1.6)	9 (1.8)
Range	4.4–13.4	4.4–11.8	5.2–13.4
MR			
Mean (SD)	0.33 (0.07)	0.31 (0.06)	0.35 (0.07)
Range	0.17–0.51	0.19–0.44	0.17–0.51
ABR 5			
UB			
Mean (SD)	0.30 (0.15)	0.25 (0.13)	0.34 (0.16)
Range	0.1–0.68	0.1–0.55	0.14–0.68
TB			
Mean (SD)	8.0 (1.9)	7.5 (1.9)	8.4 (1.9)
Range	3.7–12.4	3.7–10.2	4.7–12.4
MR			
Mean (SD)	0.30 (0.07)	0.28 (0.08)	0.32 (0.06)
Range	0.16–0.47	0.16–0.45	0.23–0.47

TABLE 5. Bilirubin-Albumin Binding Variables (mean ± SD) for Infants (n = 45) in UB Subgroup

	Normal ABR (n = 20)	Abnormal ABR (n = 25)	P Value
Peak bilirubin (mg/dL)	9.5 ± 2.2	10 ± 1.2	0.29
Peak bilirubin:albumin ratio	0.33 ± 0.08	0.39 ± 0.07	0.01
Peak UB (μg/dL)	0.40 ± 0.15	0.62 ± 0.20	0.0002

the clinical experience that premature neonates are more susceptible to bilirubin-induced neurotoxicity.[6]

One of the tools commonly used to investigate bilirubin-induced neurotoxicity in neonates is the

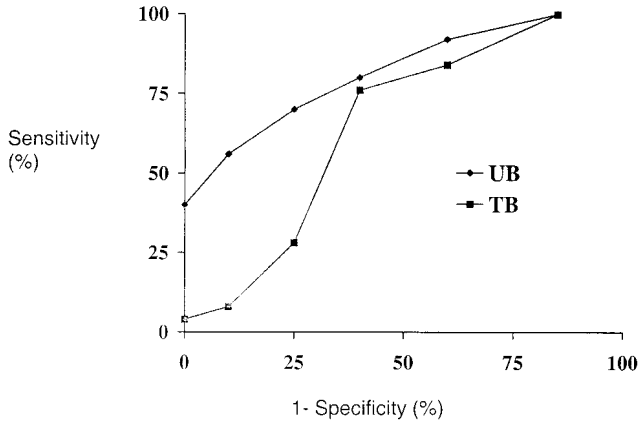

Fig 2. ROC curves predicting the risk of transient bilirubin encephalopathy using serum TB and UB values.

ABR. ABR has been studied in term and to a lesser extent in premature newborns as a direct, noninvasive neurophysiologic assessment of reversible bilirubin neurotoxicity.[10,13,14,33] These studies have demonstrated reversible changes in ABR wave III and wave V latencies induced by bilirubin. However, until now, there has been a paucity of information on sequential maturational changes in ABR during the first postnatal week in newborns ≤32 weeks' gestation for the ABR to be useful to identify bilirubin-induced encephalopathy in these infants. The ABR at this gestation was shown recently to have rapid sequential maturational changes during the first postnatal week of life.[22] Although at these ages waves III and V are not always detectable and therefore sequential measurements of latencies are not always possible, ABR waveforms can be categorized into response types, which also show progressive maturational changes during the first postnatal week.[22] These patterns can now be used to assess auditory toxicity. Our data demonstrate a strong temporal correlation of peak UB with abnormal maturation of the ABR.

Various clinical factors, such as hypothermia, hypoxia, acidosis, hypercarbia, asphyxia, sepsis, severe intraventricular hemorrhage, and hemolysis have been postulated to explain the occurrence of bilirubin neurotoxicity at much lower levels of serum TB. These factors are thought to increase the risk of kernicterus by affecting serum bilirubin-albumin binding, bilirubin entry into the brain, or tissue uptake of bilirubin. Ritter et al[21] in a prospective study identified a degree of hypoxia and acidosis that occurred before maximum UB level and that was present in newborns with kernicterus and not present in those without kernicterus. However, in 2 separate and independent retrospective analyses, Kim et al[24] and Turkel et al[25] failed to identify a single risk factor or combination of risk factors to be useful in predicting development of kernicterus in premature infants. As in earlier studies, we also found no statistically significant differences in clinical risk factors between the normal and bilirubin encephalopathy groups.

Various biochemical factors are involved in the pathogenesis of bilirubin encephalopathy. In healthy term newborns, it may be possible to estimate the UB

TABLE 6. Summary of Mean UB and Risk of Kernicterus

Study	Gestation (*n*)	Mean UB (μg/dL)		
		No Kernicterus or Normal ABR	ABR Changes	Overt Kernicterus
Current	Premature (45)	0.40	0.62	None
Ritter	Premature (30)	0.64	Not done	1.1
Cashore	Premature (13)	0.76	Not done	1.6
Nakamura	Premature (88)	0.54	Not done	1.3
Funato	Term (37)	0.78	1.34	None

from the B:A MR, as binding properties are fairly constant.[34] Amit and Brenner[5] reported dependency of bilirubin toxicity on the B:A MR in vitro using fetal rat glial cells. Similarly, the B:A MR has been shown to be more predictive of bilirubin encephalopathy than the serum TB as evaluated by ABR in term infants with hyperbilirubinemia.[12] However, in the premature newborn, the MR's usefulness is not known. Kim et al[24] found no difference in MR between kernicteric and nonkernicteric premature newborns in a retrospective analysis. In the premature infant, bilirubin binding to albumin may be affected by the presence of competitors for bilirubin binding, releasing UB at even lower B:A MRs. The studies of Kim, Ritter, and Turkel all were performed in an era in which kernicterus was very prevalent in some nurseries but not in others. This may have been associated with the common use of benzyl alcohol as a preservative in drugs and injectable saline solutions at this time. The metabolite of benzyl alcohol, sodium benzoate, is a potent displacer of bilirubin from albumin creating elevated UB while having a slight depressing effect on serum TB. A recent study also demonstrated considerable confusion about using the B:A MR by trying to correlate the ratio and the bilirubin with "bilirubin binding ability."[35,36]

Previous studies suggested that the neurologic outcome of hyperbilirubinemia correlates better with UB than serum TB levels.[11,20] Our study also found that UB is a more sensitive predictor than either serum TB or B:A MR of abnormal ABR maturation and hence bilirubin toxicity in premature newborns with hyperbilirubinemia. This suggests that these neonates with bilirubin-induced transient auditory toxicity have altered bilirubin-binding capacity. Our findings suggest a significant relationship between unbound levels and incidence of abnormal ABR maturation with significant increase in the incidence of bilirubin-induced auditory toxicity with UB levels >0.5 μg/dL. The slight overlap in UB levels between neonates with and without bilirubin encephalopathy suggests that other factors such as duration of hyperbilirubinemia, blood-brain barrier status, and neuronal susceptibility probably play an important role in some patients. All study participants passed a screening hearing test before being discharged from the nursery; however, the possibility of auditory neuropathy cannot be excluded. This transient bilirubin-induced auditory toxicity may have short-term implications. An association between abnormal ABR maturation and an increased incidence of apnea/bradycardia in these patients has been observed.[37] Long-term implications require additional investigation.

CONCLUSION

UB is a better predictor of bilirubin-induced auditory toxicity than either serum TB or B:A MR as evaluated by sequential ABRs in infants of 28 to 32 weeks' GA. Serial ABR testing can be a useful, noninvasive tool to detect early reversible bilirubin neurotoxicity in the premature newborn.

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CONTRAINDICATED USE OF CISAPRIDE: IMPACT OF FOOD AND DRUG ADMINISTRATION REGULATORY ACTION

Context. Cisapride, a gastrointestinal tract promotility agent, can cause life-threatening cardiac arrhythmias in patients susceptible either because of concurrent use of medications that interfere with cisapride metabolism or prolong the QT interval or because of the presence of other diseases that predispose to such arrhythmias. In June 1998, the US Food and Drug Administration (FDA) determined that use of cisapride was contraindicated in such patients and informed practitioners through additions to the boxed warning in the label and a "Dear Health Care Professional" letter sent by the drug's manufacturer.

Objective. To evaluate the impact of the FDA's 1998 regulatory action regarding contraindicated use of cisapride.

Conclusion. The FDA's 1998 regulatory action regarding cisapride use had no material effect on contraindicated cisapride use. More effective ways to communicate new information about drug safety are needed.

Smalley W, Shatin D, Wysowski DK, et al. *JAMA*. 2000;284:3036–3039

Noted by JFL, MD

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